ORIGINAL ARTICLE

Harmonic technology versus neodymium-doped yttrium aluminium garnet laser and electrocautery for lung metastasectomy: an experimental study

Alfonso Fiorelli[a],*, Marina Accardo[b], Emanuele Carelli[a], Assunta Del Prete[a], Gaetana Messina[a], Alfonso Reginelli[c], Daniela Berritto[c], Ferdinando Papale[d], Emilia Armenia[d], Paolo Chiodini[e], Roberto Grassi[c] and Mario Santini[a]

[a] Thoracic Surgery Unit, Second University of Naples, Naples, Italy
[b] Morphopatology Unit, Second University of Naples, Naples, Italy
[c] Radiology Unit, Second University of Naples, Naples, Italy
[d] Department of Biotechnology, Second University of Naples, Naples, Italy
[e] Medical Statistics Unit, Second University of Naples, Naples, Italy

* Corresponding author. Thoracic Surgery Unit, Second University of Naples, Piazza Miraglia, 2, 80138 Naples, Italy. Tel: +39-0815665228; fax: +39-0815665230;
   e-mail: alfonso.fiorelli@unina2.it (A. Fiorelli).

Abstract

OBJECTIVES: We compared the efficacy of non-anatomical lung resections with that of three other techniques: monopolar electrocautery; neodymium-doped yttrium aluminium garnet laser and harmonic technology. We hypothesized that the thermal damage with harmonic technology could be reduced because of the lower temperatures generated by harmonic technology compared with that of other devices.

METHODS: Initial studies were performed in 13 isolated pig lungs for each group. A 1.5-cm capsule was inserted within the lung to mimic a tumour and a total of 25 non-anatomical resections were performed with each device. The damage of the resected lung surface and of the tumour border were evaluated according to the colour (ranging from 0—pink colour to 4—black colour), histological (ranging from Score 0—no changes to Score 3—presence of necrotic tissue) and radiological (ranging from Score 0—isointense T_2 signal at magnetic resonance imaging to Score 3—hyperintense T_2 signal) criteria. A total of seven non-anatomical resections with harmonic technology were also performed in two live pigs to assess if *ex vivo* results could be reproducible in live pigs with particular attention to haemostatic and air-tightness properties.

RESULTS: In the *ex vivo* lung, there was a statistical significant difference between depth of thermal damage ($P < 0.0001$) in electrocautery (1.3 [1.2–1.4]), laser (0.9 [0.6–0.9]) and harmonic (0.4 [0.3–0.5]) groups. Electrocautery had a higher depth of thermal damage compared with that of the laser ($P = 0.01$) and harmonic groups ($P = 0.0005$). The harmonic group had a less depth of thermal damage than that of the laser group ($P = 0.01$). Also, histological damages of tumour borders ($P < 0.001$) and resected lung surface ($P < 0.001$), radiological damage of tumour borders ($P < 0.001$) and resected lung surface ($P < 0.001$) and colour changes ($P < 0.001$) were statistically different between three study groups. Resections of *in vivo* pig lungs showed no bleeding; 2 of 7 cases of low air leaks were found; however, they ceased by sealing lung parenchyma with harmonic technology.

CONCLUSIONS: Our experimental data support the resections performed with the use of harmonic technology. The lack of severe tissue alterations could favour healing of parenchyma, assure air tightness and preserve functional lung parenchyma. However, randomized controlled studies are needed in an *in vivo* model to corroborate our findings.

Keywords: Harmonic technology • Electrocautery • Laser • Lung resection • Wedge resection

INTRODUCTION

A limited pulmonary resection is performed in a non-anatomical fashion, regardless of intersegmental or interlobar planes and without individual ligation of segmental bronchovascular structures. It is usually performed as a suitable procedure for several diseases including lung metastases [1]. Stapling is the fastest method to carry out non-anatomical lung resections, but it may cause inappropriate surgical margins and loss of greater lung volume than expected in case of multiple lesions and/or close to the hilum. Monopolar electrocautery and/or 1318 wavelength neodymium-doped yttrium aluminium garnet (ND:YAG) laser are current alternatives to stapling [2, 3]. They allow removal of lung nodules by sparing as much healthy lung parenchyma as possible

and enabling to maintain a safety distance of 5 mm from the borders of metastases. However, electrocautery is unable to control haemorrhage from parenchyma and could cause severe thermal injury with increasing risks of fistula and air leaks [4]. The ND:YAG laser presents better cutting and coagulation capability than electrocautery, but its main weakness is the cost of acquisition and training for staff [5, 6].

Harmonic technology (HT; Ethicon, Johnson & Johnson Medical Ltd) was used initially in abdominal surgery for its coagulation properties [5–9] and in 1996, Aoki and Kaseda [10] introduced it to perform lung resections. HT denatures proteins into a sticky coagulum that seals the blood vessels by using ultrasonic energy. The HT also has a cutting and dissection function produced by the longitudinal vibration of the blade tip at 55 500 times per second, which has a cavitational effect facilitating dissection between planes of tissue.

Lung parenchyma is composed of blood vessels and air-filled spaces, thus the ideal device to carry out limited resections would need to provide excellent haemostatic properties and minimize thermal damage to maintain the integrity of underlying parenchyma, prevent air leaks and preserve functional lung parenchyma.

Since HT is ultrasonically activated, it generates only limited heat (temperature ranging from 50 to 100°C) compared with high-frequency technology instruments such as electrocautery and laser that produce higher temperatures (ranging between 150 and 400°C).

Thus, in this study, we compared the parenchymal damage after non-anatomical lung resection performed with three different devices: HT, electrocautery and laser with the hypothesis that HT could reduce tissue damage compared with standard devices such as electrocautery and laser and thus to be a valid alternative for performing lung resections in clinical practice.

MATERIALS AND METHODS

Study design

The first part of the study was conducted in isolated pig lungs in the laboratory of the Second University of Naples. Non-anatomical lung resections were performed using three different devices: monopolar electrocautery, ND:YAG laser and HT. The resected lung surface and the tumour were categorized into three groups based on the device that was used (electrocautery, laser and HT). The tissue damages were evaluated based on macroscopic (tissue colour), microscopic (histological and microelectronic) and radiological criteria as summarized in Table 1, and the intergroup differences statistically analysed.

In the second part of the study, non-anatomical lung resections were performed using the HT in vivo pig lungs at the Animal Research Center in Pomezia, Rome, to assess the reproducibility of ex vivo model results with particular attention to haemostatic and air-tightness properties.

All pathologists and radiologists from the Second University of Naples who reviewed the coded specimens (resected lung surface and tumour borders) were blinded to the type of instrument used.

All animals received humane care in compliance with the 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guide for the Care and Use of Laboratory Animals' [11].

Isolated pig lung model

A total of 13 isolated pig lungs were used for each group. Two non-anatomical resections, one for each lobe, were generally performed per lung to avoid that repeated resections within the same lobe could affect the results.

The ex vivo pig model was assembled as reported in Fig. 1. The intact lung was removed from freshly slaughtered pigs (weight 100–120 kg.). To simulate a metastatic nodule, a 1.5-cm capsule was implanted via a small incision in the lung parenchyma 1 cm beneath the lung surface and more than 4 cm away from fissures. The lung opening was then closed with a 3-0 suture. The tumour was grasped with atraumatic forceps and then lung tissue was resected at least 2 cm away from the tumour. Monopolar electrocautery was used at a maximum power of 50 W. The ND:YAG laser was used in a non-contact mode maintaining a distance of 2 cm from the lung surface, with a wavelength of 1318 nm and a power output of 40 W. The HT was used with a vibration frequency of 55.500 Hz; blade excursions/force of 70 μm/Level 3 and jaw surface position: blunt.

After resection, a Fogarty catheter, connected to a manometer, was inserted within main bronchus. The lung was inflated to 25–30 mmHg pressure and the resected lung surface was filled with saline water to test air tightness. An example is reported in Video 1.

Gross appearances of the lesions were documented at the time of removal (macroscopic examination). The tumour and the resected lung surface were then submitted individually for radiological and microscopic evaluation.

Macroscopic changes

The resected lung surface and the tumour borders were classified by colour as pink (expression of no-damage being similar to normal parenchyma), white (light damage), brown (moderate damage) and black (severe damage). To be able to comparable these results, each colour was then associated with a numeric score grading from 0 to 3 [2, 3] as summarized in Table 1.

Radiological changes

7T μMR (BrukerBioSpec 70/16US; Bruker Medical Systems, Ettlingen, Germany) was used to evaluate radiological changes in

Table 1: Criteria to define macroscopic, radiological and histological changes

| Variables	Damage	Definition	Score
Macroscopic	None	Pink colour	0
	Low	White colour	1
	Moderate	Brown colour	2
	Severe	Black colour	3
Radiology	None	Isointense T_2 signal	0
	Low	Hypointense T_2 signal	1
	Moderate	Inhomogeneous iso-hyperintense T_2 signal	2
	Severe	Hyperintense T_2 signal	3
Histology	None	Normal architecture without thermal damage	0
	Low	Presence of coagulative degeneration	1
	Moderate	Presence of amorphous degeneration	2
	Severe	Presence of destructive degeneration	3
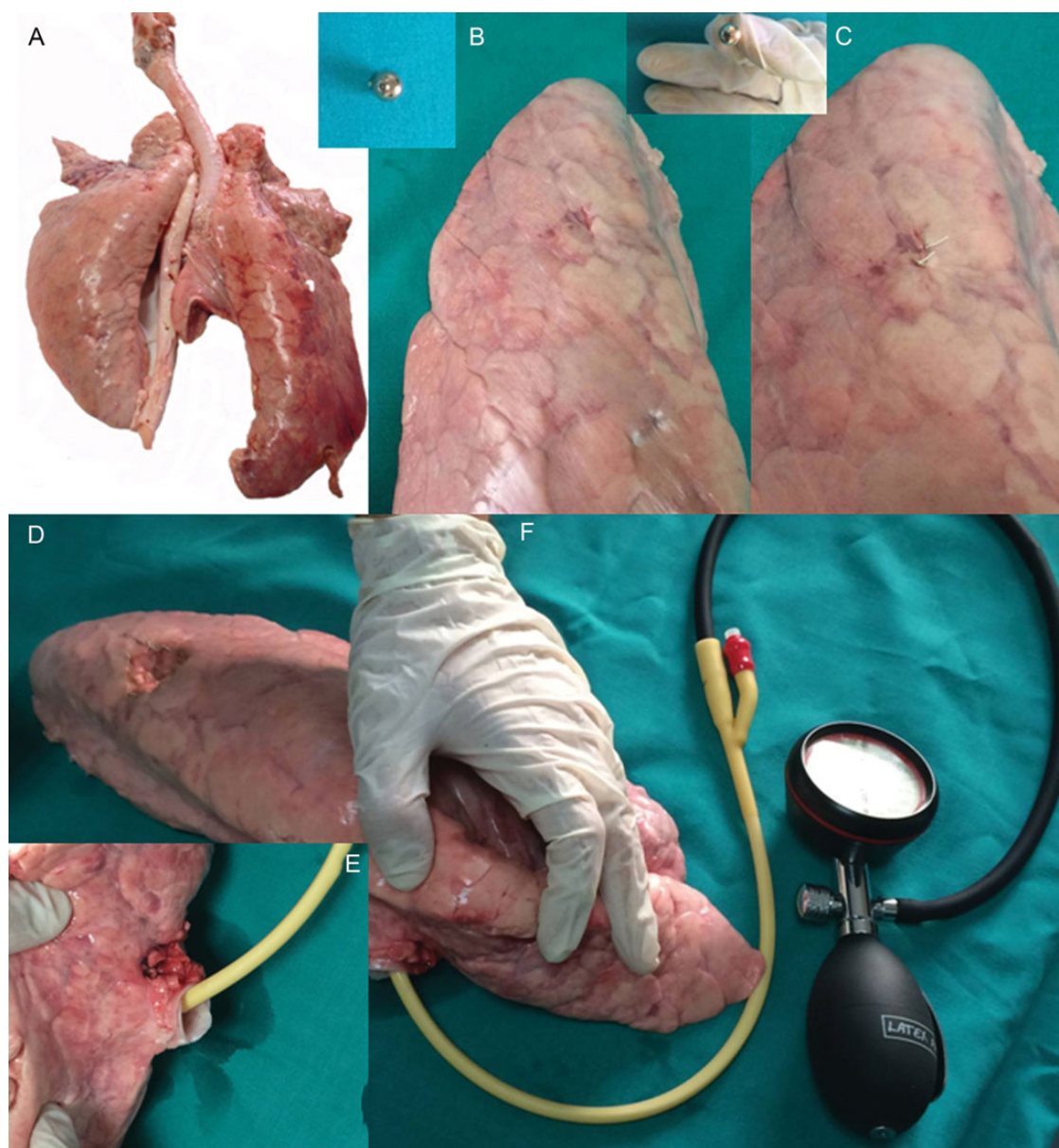
Figure 1: The intact lungs were separated from the heart and the lung specimen was removed *en bloc* from freshly slaughtered pigs (**A**). A 1.5-cm capsule (inserts) was implanted within the lung (**B**) and the parenchyma was then closed (**C**). After resection (**D**), a Fogarty catheter was inserted within the main bronchus (**E**) and connected to manometer (**F**) to inflate the lung and test air tightness.

the lung tissue surrounding the ablated lesion. A tripilot sequence along three orthogonal planes was acquired as a localizer scan for the specimen; the following parameters were used: time repetition (TR) 100.0 ms; time to echo (TE) 6.0 ms; field of view (FOV) 8.00 cm; imaging sequence (IS) 2.00 mm. Rapid acquisition with relaxation enhancement (RARE) T_2-weighted sequences in axial section were acquired in order to differentiate anatomical structures mainly on the basis of T_2 values also with suppression of fat signal: compartments filled with water appeared bright and tissues with high fat content appeared dark. The following parameters were used: TR 4200 ms; TE 36.0 ms; FOV 4–7 cm; matrix 256 * 256; IS 1.00/1.00 mm; n slices 19–35. RARE T_1: TR 1300 ms; TE 7.5 ms; FOV 7.14/4.67 cm; matrix 256 * 256; IS 1.00/1.00 mm; FOV 4–7 cm; n slices 19–35.

Magnetic resonance imaging evaluation of the lung tissue surrounding the surgical ablation was obtained by comparing T_2 signal of the resected surface and T_2 signal of the normal tissue:

T_2-weighted signal of the lung tissue adjacent to the resected surface was defined as isointense (no change—Score 0); hypointense (low change—Score 1), iso-hyperintense (moderate change—Score 2) or hyperintense (severe change—Score 3) in comparison with normal lung tissue [2, 3].

Microscopic changes

At the end of the experiments, the tumour and the resected lung surface were fixed in 10% phosphate-buffered glutaraldehyde for 24 h.

Light microscopic examination. Materials resected from the lung were dehydrated in a graded alcohol bath and were fixed with 10% buffered formalin and embedded in paraffin thereafter. Cross-sections, which were perpendicular to the resection line, were cut at a thickness of 5 µm, and stained with haematoxylin
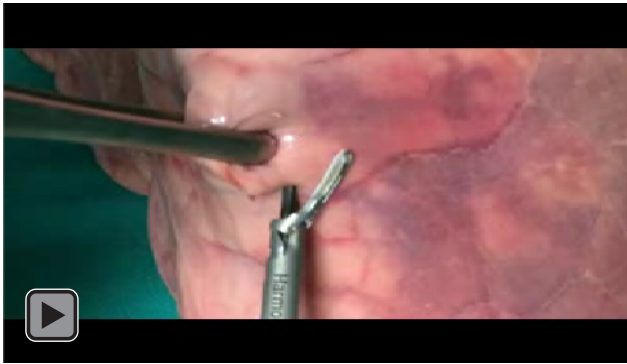
Video 1: A non-anatomical resection mimicking metastasectomy using harmonic technology in the *ex vivo* pig model is reported. The tumour was grasped with atraumatic forceps and then lung tissue was resected at least 2 cm away from the tumour using harmonic technology. After resection, the lung was inflated to 25–30 mmHg pressure with a Fogarty catheter and the resected lung surface was filled with saline water. No air leaks were found.
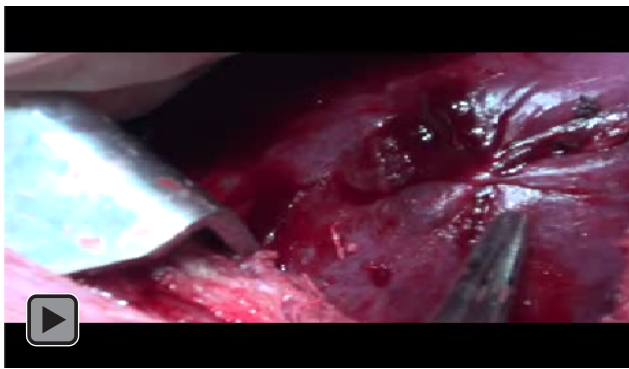
Video 2: The main steps of non-anatomical resection mimicking metastasectomy using harmonic technology in the 'in vivo' pig model are reported. The tumour was grasped with atraumatic forceps and then lung tissue was resected at least 2 cm away from the tumour using harmonic technology. The pleural cavity was filled with saline solution and the lung was reinflated under water. No air leaks were seen.

and eosin. Using a light microscopy and morphometric computer imaging analysis, the thermal depth was measured from the point of device application to the margins of unchanged nearby tissue. Histological changes were scored according to a grading system from 0 to 3: 0, normal architecture without thermal damage; 1, light thermal damage. The presence of coagulative degeneration in which much of the cellular outline and tissue architecture was still discernible and where 5–25% of the cells showed signs of thermal damage; 2, middle thermal damage. The presence of amorphous degeneration in which cells formed a continuous amorphous mass with no resemblance to the original architecture except for the presence of elastic fibres and where 40–60% of the cells showed signs of thermal damage; 3, destructive degeneration in which cells formed debris without recognizable cellular structures and where more than 70% of the cells showed signs of thermal damage [2, 3, 12]).

Scanning electronic microscopic evaluation. Samples were stained with osmic acid, dehydrated in a graded alcohol series, substituted by isopentyl acetic acid, dried with a critical-point drier and spatter-coated with ionic gold colloid. When the net formation was still discernible through the scanning electron microscope, the area was considered to be coagulative, whereas it was defined as being amorphous or necrotic when no discernible structures were present [2, 13].

Pig model

Two 35–40 kg pigs were employed to evaluate the efficacy of HT for performing non-anatomical resections, with the specific aim to assess air leakage and blood loss. The day before the experiment, the pig was brought into the laboratory for experimental surgery. During the 8 h preceding the experiment, the animal was fasted from food or water.

The pig was anaesthetized using the following sedation, relaxation and narcosis regimen: ketamine (Ketanest 10%, 20 mg/kg intramuscularly), xylazine (xylazine 2%, 2 mg/kg intramuscularly), atropine sulphate (1%, 3 ml/animal) and propofol (Disoprivan 1%, 2–5 ml/animal). A selective intubation was performed. The pig was connected to a mechanical ventilator and ventilated at a tidal volume of 10 ml/kg and a ventilation rate of 12 breaths/min. Anaesthesia was maintained with a 2–3% inhaled isoflurane–oxygen mixture. After anaesthesia, the pig was secured to an operative table, and a standard thoracotomy was performed through the fifth rib with the pig placed in a lateral position. In the same way reported for the isolated lung model, a 1.5 capsule was inserted within each lobe of the lung to simulate the tumour. The lung opening was then closed with a 3-0 suture. The tumour was then grasped with atraumatic forceps and resected using HT. The thoracic cavity was then filled with 0.9% NaCl, the lung was submerged in normal saline solution and a constant airway pressure at 25 cmH$_2$O was applied with ventilator for 5 min to detect air leaks in the resected lung surface in agreement with the standard practice of thoracic surgery.

The intensity of air leakage was scored according to a subjective grading system from 0 to 3 (0, no leakage; 1, single countable bubbles; 2, stream of bubbles; 3, coalescent bubbles) [14]. For each resection, the operative time, blood loss and air tightness were measured. At the end of the operation performed on one side, the pig was repositioned to carry out resections in the contralateral lung. An example is reported in Video 2.

The tumour specimen of tumour and the resected lung surface were placed in a container filled with 10% formalin solution and were evaluated by pathologists using the same criteria adopted for the isolated pig model.

Statistical analysis

The sample size calculation was performed only in the isolated pig model while resections in the *in vivo* pig were not supported by any sample size calculation due to the very small number of live pigs available.

The depth of thermal damage was considered as the primary outcome for sample size calculation since a minimal thermal damage clinically favours the healing of the parenchyma and reduces the risk of haemorrhage and air leaks. The total sample of 75 non-anatomical resections (25 for each of the three groups) achieves 80% power to detect differences among the means versus the alternative of equal means using an *F*-test with a 5% significance level. The size of the variation in the means is represented by their standard deviation (SD) that is 0.37 and the common SD within a group is assumed to be 1.00.

The Kolmogorov–Smirnov test and graphic histograms were used to check the normality/skewness of continuous variable data in subgroups before further analysis, and appropriate statistical tests have been chosen accordingly. Data were summarized as mean and SD for normally distributed continuous variables;

median and interquartile range (25th–75th percentiles) for skewness continuous variables or absolute number and percentage for categorical variables, as appropriate. Differences between subgroups were compared using the χ^2 test for categorical variables; one-way ANOVA test for symmetric continuous variables and Kruskal–Wallis test for skewness continuous variables, with *post hoc* test if indicated. A *P*-value <0.05 was considered statistically significant. MedCalc statistical software (Version 12.3, Broekstraat 52; 9030 Mariakerke; Belgium) was used for analysis.

RESULTS

Each study group of isolated lung model included a total of 25 non-anatomical resections. In three lungs, one for each group, only one resection instead of two was performed because the other lobes were damaged during their removal from freshly slaughtered pigs. The cut lines, the weight of resected tumour and operative time were similar between three groups without significant differences (Table 2).

Macroscopic findings

The results are summarized in Table 3. The electrocautery group showed a significant colour change in the resected lung surface and in the tumour borders compared with the HT and laser group.

HT showed a less evident colour change compared with laser, but it did not reach significant difference.

Interestingly, HT group did not show brown and/or black parenchyma changes compared with the electrocautery and laser groups. An example is reported in Fig. 2.

After inflation of the lung, the rates of air leaks were lower ($P < 0.0001$) in HT (4/25; 16%) compared with laser (21/25; 84%) and electrocautery (24/25; 96%).

Radiological findings

The results are summarized in Table 2. The capsule implanted within the lung was readily visible on T_2-weighting MRI images as round masses.

In the electrocautery group, the tumour borders and resected lung surface were irregular and hyperintense at T_2-weighting indicating severe tissue damage graded as 3, whereas in the laser and HT groups they were well delineated without important signal change. An example is reported in Fig. 3.

Table 2: Comparison of groups

Variables	Groups			*P*-value
	Harmonic	Laser	Electrocautery	
Length of cut lines (cm)	4.6 ± 0.7	4.5 ± 0.6	4.5 ± 0.9	0.8
Weight of resected tumour (g)	119 ± 29	116 ± 59	118 ± 81	0.7
Operative times (min)	5 ± 2	9 ± 4	6 ± 3	0.3

P-value was calculated with the ANOVA test. Data are reported as mean ± standard deviation.

Microscopic findings

Depth of thermal damage. The median depth of thermal damage in the electrocautery, laser and harmonic groups was: 1.3 [1.2–1.4], 0.9 [0.6–0.9] and 0.4 [0.3–0.5] mm, respectively. There was a statistically significant difference between groups ($P < 0.0001$; Kruskal–Wallis test). *Post hoc* test showed that the depth of thermal damage in the electrocautery group was higher than that in the laser ($P = 0.01$) and harmonic groups ($P = 0.0005$). In addition, the harmonic group had a less depth of thermal damage than the laser group ($P = 0.01$). An example is reported in Fig. 4.

Light microscopic evaluation. The results are given in Table 3. Severe histological damage (Grade 3) with destructive degeneration of parenchyma was observed in 52% of specimens of the electrocautery group, whereas specimens of the laser and HT groups presented coagulative or amorphous tissue without signs of destructive degeneration.

The resected lung surface in the electrocautery group underwent profound modifications. There were large areas of amorphous material with complete loss of alveolar structure and fusion of different cell components. The cells were oedematous and whitish, demonstrating signs of severe thermal damage, equivalent to tissue damage score 3.

The resected lung surface in the laser group showed moderate tissue damage. The alveoli were larger than normal due to the presence of amorphous material.

The lung surface cut with HT showed increased eosinophil cells as a result of an acute traumatic effect without signs of necrosis and vascular endothelial injury. The alveoli had a normal architecture and other elements, such as vessels and bronchus, were well evident. An example is reported in Fig. 5.

There was a significant association between the colour changes and the different histological damages ($P < 0.0001$; χ^2 test). Among the pink samples ($n = 16$), 15/16 (94%) coagulative, 1/16 (6%) amorphous degeneration and no case of destructive degeneration were found. Among the white samples ($n = 34$), 21/34 (62%) showed coagulative, 13/34 (38%) amorphous degeneration and no case of destructive degeneration was found. Of the brown samples ($n = 19$), 11/19 (58%) amorphous degeneration and 8/19 (42%) destructive degeneration were found. All black samples ($n = 6$) presented destructive degeneration.

Electronic microscope scanning evaluation. The resected lung surface appeared to be deeply altered with disruption of alveolar architecture and fusion of the different cell components in the electrocautery and laser group. Such findings were rarely present in the HT group. Also, the depth of this kind of alteration was higher in the electrocautery and laser group compared with that in the HT group. An example is shown in Fig. 4.

In vivo model

A total of seven wedge resections using HT were performed in two *in vivo* pigs. We generally performed two resections per lung (one for each lobe) except in one lung where only one resection was achieved because the other lobe was damaged during thoracotomy.

The mean time for resection was 7 ± 4.3 min. No bleeding occurred during dissection and no additional haemostatic materials were required. After resection, no additional sutures or haemostatic materials were used to achieve air tightness. In only 2/7

Table 3: Differences between study groups

Groups	No. of samples	Variables				Score	P-value
		Macroscopic changes					
		Pink	White	Brown	Black		
Resected surface							
Electrocautery	25	0	1	18	6	2 [2–2.2][a]	<0.001*
Laser	25	5	19	1	0	1 [1–1.2][b]	
Harmonic	25	11	14	0	0	1 [0–1][c]	
Tumour borders							
Electrocautery	25	0	3	19	3	2 [2–2.1][a]	<0.001*
Laser	25	8	16	1	0	1 [1–1.1][b]	
Harmonic	25	14	11	0	0	1 [0–1][c]	
		Radiological changes					
		1	2	3			
Resected surface							
Electrocautery	25	0	15	10		2 [2–2.1][a]	<0.001*
Laser	25	17	7	1		1 [1–1.1][b]	
Harmonic	25	23	2	0		1 [0–1][c]	
Tumour borders							
Electrocautery	25	0	16	9		2 [2–3][a]	<0.001*
Laser	25	18	7	0		1 [1–1.2][b]	
Harmonic	25	21	4	0		1 [0–1.1][c]	
		Histological changes					
		Coagulative	Amorphous	Destructive			
Resected surface							
Electrocautery	25	0	12	13		3 [2–3][a]	<0.001*
Laser	25	15	9	1		1 [1–2][b]	
Harmonic	25	21	4	0		1 [0–1.2][c]	
Tumour borders							
Electrocautery	25	0	16	9		2 [2–3][a]	<0.001*
Laser	25	18	7	0		1 [1–2.1][b]	
Harmonic	25	23	2	0		1 [1–1.1][c]	

Scores are reported as median and interquartile range (25th–75th percentiles).
*The *P*-value between three study groups was calculated using the Kruskal–Wallis test. *Post hoc* test showed that significant difference between a versus b (*P* = 0.005); a versus c (*P* = 0.001); but no significant difference between b versus c (*P* = 0.078).

cases, Grade 1 air leaks were seen that ceased by sealing the lung parenchyma with HT. In the other 5/7 cases, no air leaks occurred.

Histological examinations showed deep thermal damage of 0.3 ± 0.2, lower than that observed in the *ex vivo* model despite the fact of not being significant (*P* = 0.70). The underlying parenchyma showed a normal structure; the resected lung surface was composed of fibrinoid tissue, the vessel appeared to be closed as well as the small bronchioles.

DISCUSSION

Electrocautery and laser are widely used as alternatives to staplers to perform non-anatomical lung resections. The electrocautery (EC) implies the flow of alternating current at high frequency and high voltage through the tissue, where the patient becomes a part of the electric circuit. Electrosurgical coagulation occurs by excessive heating and charring of the tissue that form a scar, thereby achieving the haemostatic effect [15]. However, it cannot control bleeding and air leaks from medium-sized to large vessels and bronchi [4, 15].

In 1967, Minton *et al.* [16] demonstrated the effects of Nd:YAG laser on pulmonary parenchyma and excised a tumour in an experimental model. Since that time, the use of laser in thoracic surgery has widely increased and different wavelengths of lasers were explored with particular emphasis on lung-sparing surgery (mainly metastasectomy). Rolle *et al.* [17] compared the effect of 1.064 and 1.318 nm wavelengths and found that the coagulation qualities of the 1.318 nm wavelength were much more feasible for lung resection. After the resection of 3.267 lung nodules, 1.318 Nd:YAG laser provided simultaneously the three qualities (cut, coagulated and seal) needed for deep parenchymal resection due to a 10-fold higher absorption in water and only a one-third of extinction in blood [18]. Yet, laser was used also for other indication as the resection of interlobar fissures during lobectomy as reported by Marulli *et al.* [19]. However, the cost of acquisition and the staff training limited the use of laser in clinical practice.

The HT is an ultrasonic surgical instrument for cutting and coagulating tissue developed initially for abdominal surgery. In the last year, increasing studies [10, 20, 21] reported its use also in thoracic surgery. The working principle of the HT is that it converts mechanical energy from the high-frequency friction to heat at the blade–tissue interface and thus controls bleeding by coaptive coagulation at temperatures ranging from 50 to 100°C. Conversely, EC and laser lead to local coagulation sealing and covering the resected surfaces by burning at temperatures between 150 and 400°C.
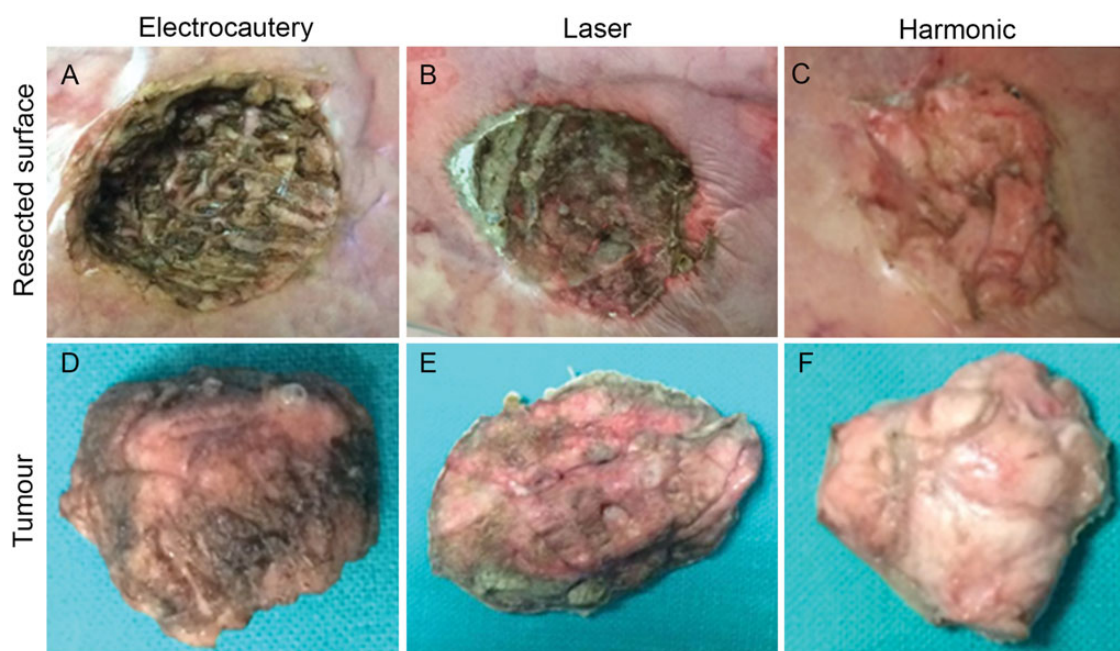
Figure 2: The differences between the devices used are visible macroscopically by observing the resected lung surface (**A–C**) and the tumour borders (**D–F**). The central crater and the periphery of resected lung surface showed black colour after electrocautery resection (A); brown colour after laser resection (B) and pink colour after harmonic resection (C). The tumour's margins presented a black colour after electrocautery resection (D); brown colour after laser resection (E) and pink colour after harmonic resection (F).
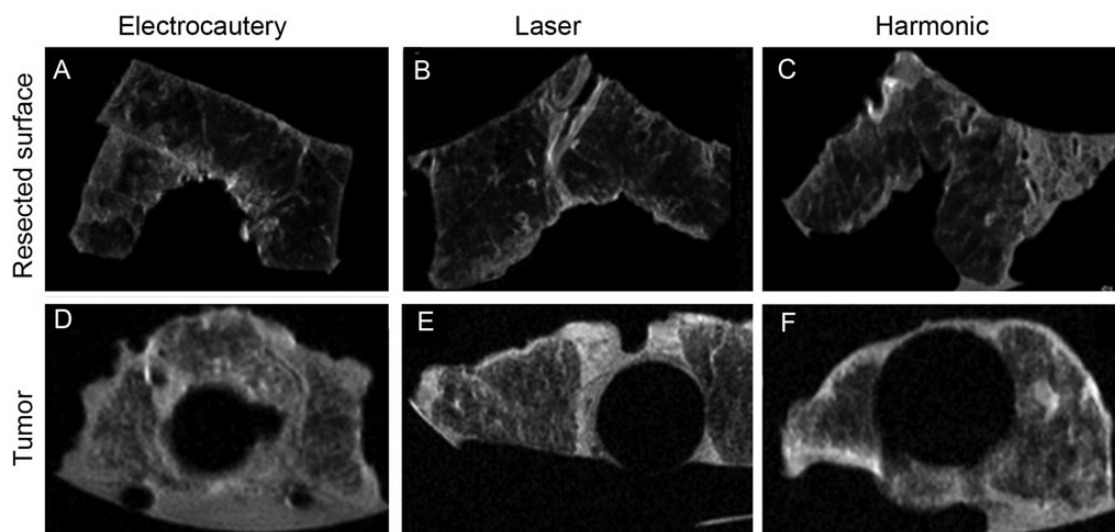

Figure 3: 7-Tesla magnetic resonance imaging evaluation of the samples. Different radiological changes in the resected lung surface (**A–C**) and the tumour borders (**D–F**) were found according to the device used. The central crater and the periphery of resected lung surface showed hyperintense T_2 signal after electrocautery resection (A); inhomogeneous iso-hyperintense T_2 signal after laser resection (B) and isointense T_2 signal after harmonic resection (C). The resected tumour presented in all cases (D–F) a round mass due to the implantation of capsule. The tumour's margins presented hyperintense T_2 signal after electrocautery resection (D); inhomogeneous iso-hyperintense T_2 signal after laser resection (E) and isointense T_2 signal after harmonic resection (F).

Since HT disperses lower energy to surrounding tissue during activation compared with EC and laser, we hypothesized that HT minimized thermal damage compared with EC and laser during non-anatomical lung resections. Despite the use of HT in lung surgery date back to 1996, no papers before the present have evaluated this issue.

To test our hypothesis, in the first part of the study, we used an experimental model consisting of isolated lung removed from freshly slaughtered pigs. A metastasectomy was performed with each device and the macroscopic, microscopic and radiological changes were compared. We focused our analysis on resected lung surface and tumour margins considering that the severe alteration of parenchyma prevented healing of the lung with prolonged air leaks, whereas the severe damage of tumour margins could render histological analysis challenging to define the resection as R0 or R1.

Our results showed that HT-related thermal injury was limited to the resected lung surface while, as shown by radiological findings, the underlying parenchyma preserved a normal architecture. In addition, microscopic examination showed that a thickened
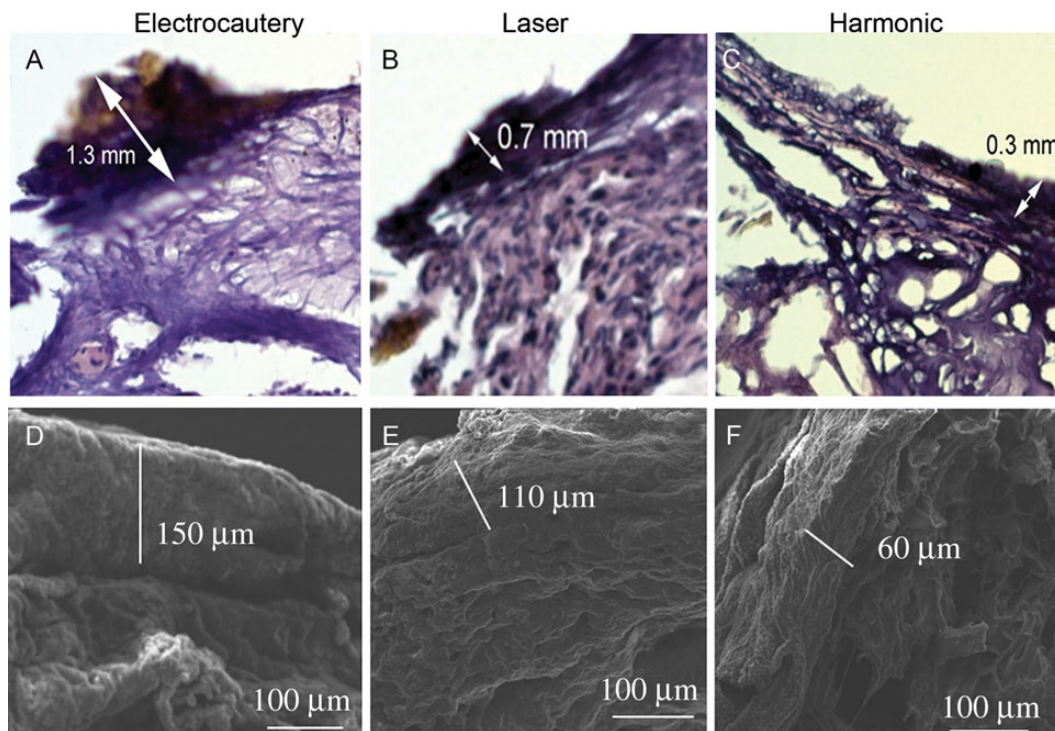
Figure 4: Morphometric computer imaging analysis on light microscopy showed that electrocautery resection (**A**) had deeper thermal damage (white arrow) than laser (**B**) and harmonic resections (**C**) (H&E staining ×40 magnification). These data were also confirmed by scanning electronic microscopy. The underlying lung tissue after electrocautery (**D**) and laser (**E**) resections showed disruption of alveolar architecture and fusion of cell components, whereas harmonic resection showed the presence of cavities resembling the normal alveoli (**F**).
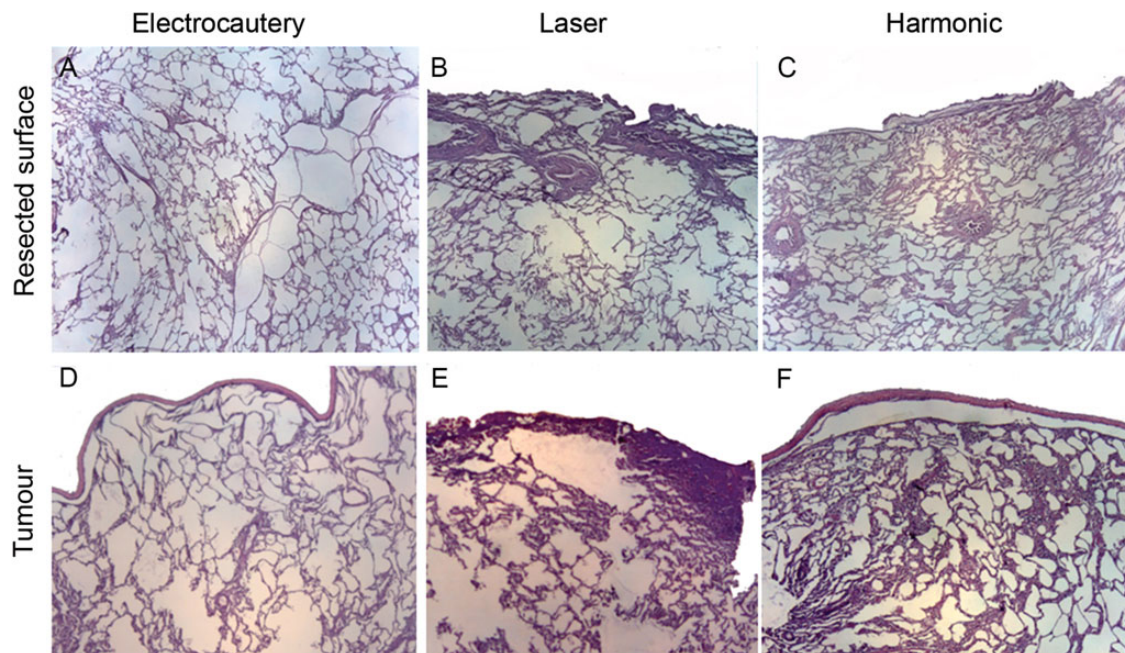

Figure 5: Different histological changes in the resected lung surface (**A**–**C**) and the tumour borders (**D**–**F**) were found according to the device used. Electrocautery resection showed a severe damage for the presence of large zones of amorphous material with complete loss of alveolar structure and fusion of different cell components (A) (H&E staining ×20 magnification). After laser resection, the alveoli were larger than normal for the presence of amorphous material. Despite present, the bronchus was not well recognized (B) (H&E staining ×20 magnification). Harmonic resection showed eosinophile cells as a result of acute traumatic effect without necrosis and/or vascular endothelial injury. The alveoli had a normal architecture, and vessels and bronchus were well evident (C) (H&E staining ×20 magnification). The tumour borders showed destructive degeneration after electrocautery resection (D); amorphous degeneration after laser resection (E) and normal architecture without thermal damage after harmonic resection (F).

cellular wall consisting of coagulative tissue covered the resected lung surface. Alveoli are fine, air-filled, sack-like structures with average wall thickness of less than 10 µm and diameters of ∼30 µm. During resection with HT, the alveolar walls are heated and they contract with consequent collapse that enhances sealing by developing coagulative tissue. Mechanical reinforcement from the coagulative effect and sealing of the alveoli allow a complete closure of the resected line, thus avoiding formation of parenchymal fistula which can induce air leaks.

Conversely, EC and laser presented a deeper thermal damage. The underlying lung parenchyma showed moderate change after laser resection and the presence of amorphous tissue at the level of resected lung surface due to the contraction of the elastic and collagen fibres induced by a photothermal reaction. On the other hand, necrotic tissue with complete alteration of the architecture of lung parenchyma was observed in the electrocautery group.

Holub *et al.* [22] reported no significant difference in terms of coagulation necrosis after the resection of ovarian and uterine samples with HT and electrocautery. In contrast, Cakan *et al.* [15] and Hayashi *et al.* [23] found that HS minimized thermal injury compared with electrocautery in thoracic surgery, as in the present study.

The different results were probably due to different characteristics of lung parenchyma in uterine and ovarian tissue. The lung is composed of alveoli that are air-filled cavities and by large amount of vessels that make it more sensitive to the high temperature generated by electrocautery.

In agreement with our results, other two studies confirmed the reduction of lung tissue damage of laser compared with that of electrocautery. In 1987, Cole and Wolfe [12] studied the effects of laser and EC on pulmonary parenchyma dogs and the mechanism of healing at different time from surgery. They found that laser caused less fibrous reaction than EC in the healing process. Kirschbaum *et al.* [3, 24] found severe thermal damage upon microscopic and radiological evaluation after lung resection with monopolar cutter compared with laser.

An interesting information was the significant association between colour changes and tissue damage. Resected lung surface with pink colour mostly presented coagulative damage but any destructive degeneration, whereas brown and/or black specimens mostly presented amorphous or necrotic tissue. Similarly, Sawabata *et al.* [2] found a significant correlation between colour changes and histological damages of the pleura ablated with ND:YAG laser. This information may be relevant for surgeons in clinical practice. In fact, in the presence of brown or black lung surface after resection, a reinforcement of the sealed line at the potential leak site with suturing and/or the use of other materials such as fibrin glue would be required to prevent air leaks.

Similar to resected lung surface, the tumour borders presented minimal tissue damage after HT resection compared with that of other devices. It may be relevant in clinical practice since the presence of necrotic tissue within tumour borders may be misdiagnosed as atypical tissue, thus creating a challenging diagnosis of R0 resection.

Although our experimental model was able to compare the radiological, macroscopic and microscopic changes between the different devices, it presented, however, important limitations such as the lack of blood flow, alveolar volume and all physiological conditions present during operation in humans. Thus, in the second part of the study, we performed a similar procedure in a live pig model using only HT which aimed to assess the haemostasis and air-tightness, which are two crucial elements to support the use of HT in thoracic surgery.

The setting of HT was an output power of 3 with an application time of not more than 5 s since Družijanić *et al.* [7] reported severe thermal damage with higher power and longer application time.

During resection, no intraoperative bleeding was seen confirming the coagulative properties of HT. In addition, in 72% of cases, no intraoperative air leaks were seen and in the remaining 28% they ceased by closure of the bronchial holes with HT. Conversely, Rolle and colleagues [17, 18] reported that during metastasectomy with laser, it was necessary to suture the medium-sized and large arteries and bronchi within the centre of a lobe. In addition, for reconstruction of the lobe and creation of a new pleural surface, a running suture re-approximated the cut edges of the pleura.

Deep thermal damage was lower than that observed in the isolated lung model. The underlying parenchyma showed normal structure; the resected lung surface was composed of fibrinoid tissue, the vessel appeared to be closed as well as the small bronchioli. The reduced thermal damage and the sealing of parenchymal tissue caused by HT were well evident in the *in vivo* model compared with the *ex vivo* pig since they were supported by a physiological healing mechanism.

Cole and Wolfe [12] reported that coagulation created intensive fibrosis that protected against air leaks, as in our study. Other experimental and clinical studies confirmed these results [10, 20, 21].

Molnar *et al.* [8] found no significant difference in air tightness and control of bleeding after lung resection with HT and a stapler in live dogs; however, histological examination found that the HT resection line presented a tissue closer to normal without granuloma formation compared with that of stapler.

Eichfeld *et al.* [20] resected 24 lung metastases from 18 patients using HT. They found vital lung tissue with intra-alveolar erythrocytes, as well as undamaged normal lung parenchyma within a distance of 0.3 cm from the cutting edge. Small- and medium-sized bronchi were mostly unaffected, the cartilaginous and glandular structures in the bronchial wall were thermally undamaged and extended necrosis and/or inflammatory infiltration was not found.

The results of our study may provide a few suggestions for clinical practice as follows. The use of electrocautery should be minimized when attempting lung resection since it causes severe destruction of lung parenchyma and does not provide a sufficiently durable safety zone of air tightness. HT seems to reduce thermal damage compared with laser. In addition, it needs no special training or preparatory measure as in the case of laser; there are no vaporization fumes that are unavoidable during parenchyma dissection with laser, and it is available in most operative rooms conversely to laser that is available only in few centres. In addition, HT did not leave behind metal foreign bodies in the surgical field that may cause late complications such as surgical staples. The smaller profile jaw of the HT blunt tip allows the surgeon to follow the outline of the tumour with parenchymal sparing. Thus, significantly more metastases can be resected which allows saving of the involved lobe and its function. However, we must always keep in mind that the active blade of HT should be kept away from any adjacent vital structure during sealing because Yamada *et al.* [25] have highlighted the potential for serious injury of the active blade in an animal model.

Study limitations

We are well aware that our data should be considered cautiously due to the following limitations of our study.

All experiments were performed on normal lung parenchyma and they should be tested if similar results could be reproducible in patients with underlying lung disease such as emphysema.

In addition, histological and radiological changes, haemostatic and airtight properties of HS were evaluated immediately after resection, whereas the effects of delayed lung injury that develop over time following the exposure were not assessed.

It would be important to conduct comparative studies in the *in vivo* model rather than just using only HT for lung metastasectomy so that bleeding and air leaks can be compared in an *in vivo* situation for all techniques. However, the limited number of pigs available and the fact that the evaluation of bleeding and air leaks after lung resection with EC and laser were largely explored in other previous studies, allowed us to evaluate only the properties of the HT in an *in vivo* model.

Finally, both of our models present some limitations that may affect the results especially in terms of air leak evaluation. In the isolated lung, the lung re-expansion was obtained by inflating the lung through a Foley catheter rather than using a ventilator. In the *in vivo* pig model, a subjective method was used to quantify the air leaks rather than a more objective strategy, such as digital drainage.

CONCLUSIONS

Our experimental data support the use of HT to achieve non-anatomical lung resections. Compared with other standard devices, HT is easier to use, avoids damage to surrounding structures and does not require special training. The lack of severe tissue alterations favours healing of parenchyma, ensures air tightness, preserves functional lung parenchyma and avoids mistakes during histological examination (i.e. necrotic area misdiagnosed as cancer). However, randomized controlled studies are needed in the *in vivo* model to corroborate our findings.

Conflict of interest: none declared.

REFERENCES

[1] Lang-Lazdunski L. Surgery for nonsmall cell lung cancer. Eur Respir Rev 2013;22:382–404.
[2] Sawabata N, Nezu K, Tojo T, Kitamura S. In vitro study of ablated lung tissue in Nd:YAG laser irradiation. Ann Thorac Surg 1996;61:164–9.
[3] Kirschbaum A, Braun S, Rexin P, Bartsch DK, Seyfer P. Comparison of local tissue damage: monopolar cutter versus Nd:YAG laser for lung parenchyma resection. An experimental study. Interact CardioVasc Thorac Surg 2014;18:1–6.
[4] Sugimoto S, Toyooka S, Iga N, Furukawa M, Sugimoto R, Shien K et al. Use of a vessel sealing system versus conventional electrocautery for lung parenchymal resection: a comparison of the clinicopathological outcomes in porcine lungs. Surg Today 2014;44:540–5.
[5] Perko Z, Pogorelić Z, Bilan K, Tomić S, Vilović K, Krnić D et al. Lateral thermal damage to rat abdominal wall after harmonic scalpel application. Surg Endosc 2006;20:322–4.
[6] Pogorelić Z, Perko Z, Druzijanić N, Tomić S, Mrklić I. How to prevent lateral thermal damage to tissue using the harmonic scalpel: experimental study on pig small intestine and abdominal wall. Eur Surg Res 2009;43:235–40.
[7] Družijanić N, Pogorelić Z, Perko Z, Mrklić I, Tomić S. Comparison of lateral thermal damage of the human peritoneum using monopolar diathermy, Harmonic scalpel and LigaSure. Can J Surg 2012;55:317–21.
[8] Molnar TF, Szantó Z, László T, Lukacs L, Horvath OP. Cutting lung parenchyma using the harmonic scalpel—an animal experiment. Eur J Cardiothorac Surg 2004;26:1192–5.
[9] Samancilar O, Cakan A, Cetin Y, Cagirici U, Veral A, Zeytunlu M et al. Comparison of the harmonic scalpel and the ultrasonic surgical aspirator in subsegmental lung resections: an experimental study. Thorac Cardiovasc Surg 2007;55:509–11.
[10] Aoki T, Kaseda S. Thoracoscopic resection of the lung with the ultrasonic scalpel. Ann Thorac Surg 1999;67:1181–3.
[11] National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals. 8th edn. Washington, DC: National Academies Press, 2011.
[12] Cole PH, Wolfe WG. Mechanisms of healing in the injured lung treated with the Nd-YAG laser. Lasers Surg Med 1987;6:574–80.
[13] Scanagatta P, Pelosi G, Leo F, Furia S, Duranti L, Fabbri A et al. Pulmonary resections: cytostructural effects of different-wavelength lasers versus electrocautery. Tumori 2012;98:90–3.
[14] Lang G, Csekeö A, Stamatis G, Lampl L, Hagman L, Marta GM et al. Efficacy and safety of topical application of human fibrinogen/thrombin-coated collagen patch (TachoComb) for treatment of air leakage after standard lobectomy. Eur J Cardiothorac Surg 2004;25:160–6.
[15] Cakan A, Cagirici U, Cikirikcioglu M, Posacioglu H, Veral A. The histological effect of harmonic scalpel and electrocautery in lung resections. An experimental study in a rat model. J Cardiovasc Surg 2004;45:63–5.
[16] Minton JP, Andrews NC, Jesseph JE. Pulsed laser energy in the management of multiple pulmonary metastases. J Thorac Cardiovasc Surg 1967;54:707–13.
[17] Rolle A, Pereszlenyi A, Koch R, Bis B, Baier B. Laser resection technique and results of multiple lung metastasectomies using a new 1,318 nm Nd:YAG laser system. Lasers Surg Med 2006;38:26–32.
[18] Rolle A, Pereszlenyi A. Laser resection of lung metastasis. Multimed Man Cardiothorac Surg 2005. doi:10.1510/mmcts.2004.000570.
[19] Marulli G, Droghetti A, Di Chiara F, Calabrese F, Rebusso A, Perissinotto E et al. A prospective randomized trial comparing stapler and laser techniques for interlobar fissure completion during pulmonary lobectomy. Lasers Med Sci 2013;28:505–11.
[20] Eichfeld U, Tannapfel A, Steinert M, Friedrich T. Evaluation of ultracision in lung metastatic surgery. Ann Thorac Surg 2000;70:1181–4.
[21] Tanaka T, Ueda K, Hayashi M, Hamano K. Clinical application of an ultrasonic scalpel to divide pulmonary vessels based on laboratory evidence. Interact CardioVasc Thorac Surg 2009;8:615–8.
[22] Holub Z, Jabor A, Sprongl L, Kliment L, Fischlová D, Urbánek S. Inflammatory response and tissue trauma in laparoscopic hysterectomy: comparison of electrosurgery and harmonic scalpel. Clin Exp Obstet Gynecol 2002;29:105–9.
[23] Hayashi A, Takamori S, Matsuo T, Tayama K, Mitsuoka M, Shirouzu K. Experimental and clinical evaluation of the harmonic scalpel in thoracic surgery. Kurume Med J 1999;46:25–9.
[24] Kirschbaum A. Nd:YAG laser surgery of lung metastases. Photonics Lasers Med 2015;4:233–9.
[25] Yamada S, Yoshino K, Inoue H. New-model ultrasonically activated shears for hemostatic sectioning during video-assisted thoracic surgery. Gen Thorac Cardiovasc Surg 2007;55:518–20.